# M E M O R A N D U M

**Department of Health and Human Services**
**Public Health Service**
**United States Food and Drug Administration**
**Center for Biologics Evaluation and Research**

**To:** Administrative File for BLA (**STN 125523/0**)
Sonday Kelly, Regulatory Project Manager, RPMS/IOD/OBRR

**From:** Alexey Khrenov, PhD, Chair, Senior Staff Fellow, LH/DHRR/OBRR

**Through:** Tim Lee, PhD, Acting Chief, LH/DHHR/OBRR

Basil Golding, MD, Director, DHRR/OBRR

**Subject:** Final review of the CMC sections in ProFibrix's original BLA for Fibrin Sealant (Human) [Raplixa]

## RECOMMENDATION

All CMC reviewers conclude that ProFibrix has provided sufficient data and comprehensive information on Chemistry, Manufacturing and Controls (CMC) for Fibrin Sealant (Human) [Raplixa], and adequately responded to all the information requests to support the approval of the BLA. We consider the manufacturing process for Raplixa to be adequately validated at the commercial scale, and sufficiently controlled to assure consistent manufacture of the commercial product that meets release specifications. All the issues identified during the inspection of b)(4) have been satisfactorily addressed.

Therefore, from the CMC perspective, we recommend **APPROVAL** of the BLA for Raplixa.

## EXECUTIVE SUMMARY

1. Early development studies and risk management tools were used to identify critical process parameters (CPPs) and manufacturing unit operations that can impact the critical quality attributes (CQAs) of intermediates and final drug product (FDP). The submitted information supported the establishment of FDP specifications and manufacturing controls to develop the manufacturing process. Each of the process parameters used in the manufacturing process was evaluated to assess its impact on the identified CQAs. All CPPs which can affect the CQAs were identified, and adequate control strategies were developed and implemented. Since the Raplixa FDP is manufactured by blending spray-dried thrombin and fibrinogen powders, the specifications for these intermediates are critically important. As requested by the FDA during the review, the justifications for in-process control (IPC) specifications were re-evaluated and the acceptance criteria were

revised based on manufacturing experience for the following parameters: (b)(4) for spray-dried thrombin; fibrinogen content, (b)(4) for spray-dried fibrinogen. Additionally, the tests for (b)(4) contents were added to the specifications of the intermediates. All (b)(4) were validated in prospective stability studies that demonstrated that the quality-defining characteristics of the intermediates were not negatively affected within the established time periods. The selected CPPs and IPC specifications provide adequate control over the manufacturing process and its robustness in delivering product batches of consistent yield, purity and potency.

2. The commercial manufacturing process has been defined using a development strategy based on the principles of (b)(4) Emphasis was put on using information gained from process development studies to identify potential CQAs of spray-dried fibrinogen and thrombin and intermediate blends that were linked to the CQAs of Raplixa FDP. Risk management and data evaluation were subsequently used to identify the CPPs and the unit operations that could impact the CQAs of Raplixa intermediates and FDP. Following process design, reviews of the manufacturing process and risk assessment of all steps were undertaken to identify control strategies to ensure consistent, reproducible process performance and FDP quality. Statistical comparisons of CQAs were made using a (b)(4) for the spray-dried intermediates and FDP. Overall, statistical analyses confirmed comparability of spray-dried fibrinogen and thrombin intermediates and Raplixa FDP manufactured at (b)(4). In total, (b)(4) consecutive PPQ batches (b)(4) intermediate blend batches filled into (b)(4) FDP lots) were successfully produced at commercial scale, under a prospective process validation protocol, to demonstrate process consistency at (b)(4), the intended commercial manufacturing site. The results demonstrated the capability of the process to routinely produce FDP batches with the desired quality attributes, and also provided evidence of process consistency and robustness.

3. (b)(4) of fibrinogen and thrombin, and absence of premature conversion of fibrinogen to fibrin were confirmed by (b)(4) (for fibrinogen) and (b)(4) (for thrombin). The desired (b)(4) Additionally, although thrombin is supplied by (b)(4) and is a licensed product, ProFibrix performed characterization studies of this material, including analysis of (b)(4) by (b)(4), characterization of protein impurities by (b)(4), and characterization of aggregates by (b)(4). The current manufacturing process for Raplixa was used for the manufacture of Phase 3 clinical batches. In early stage of product development, (b)(4). also used a similar process. The difference is that it was not performed under (b)(4) and the FDP was (b)(4). ProFibrix compared the (b)(4) product (Phase 2) and the (b)(4) aseptically manufactured product (Phase 3). In addition to the characterization methods described above, the studies included assessment of (b)(4) The test results demonstrated comparability between

Raplixa batches used in the nonclinical and clinical studies and commercial product. The material used in Phase 3 clinical trials is representative of that manufactured by the commercial process.

4. The specification for Raplixa FDP is established in accordance with ICH Guidelines Q6A and Q6B. The parameters are selected from CQAs determined in the process development studies and risk assessments. Acceptance ranges/limits are established based on manufacturing capability, clinical outcome, analytical variability, and stability data. Manufacturing capability was assessed through analysis of release data for the Phase 3 clinical and process validation batches. The following substantive issues were resolved in the course of the review:

    - Justification of Specification for Raplixa FDP submitted in the original BLA was deemed insufficient. Initially, key parameters of specification were established arbitrarily and not based on manufacturing capability. As requested by FDA, the ranges and limits for quantitative parameters in the specification were re-evaluated based on statistical analysis of the data acquired from testing all FDP lots. As a result of the analysis, the specification limits for the following parameters were modified: fibrinogen potency, fibrinogen content, moisture content, and endotoxin.

    - The original specification for Raplixa included the Phase Purity - (b)(4) The test was developed at the IND stage in response to FDA request as a secondary control of the moisture content in the product. Review of the data submitted in the BLA demonstrated that (b)(4) is not sensitive enough to detect changes in trehalose (b)(4) associated with the moisture content within or slightly above of the specification limit. Considering that the primary test for moisture content (b)(4) was demonstrated to be sufficiently sensitive for controlling this parameter and that an (b)(4) test was developed for controlling premature fibrinogen activation, (b)(4) test was removed from the Raplixa specification.

    The FDP Release Specification in Table 2 is considered adequate to control the identity, purity, biological activity, and safety of Raplixa. As the specification is (b)(4) based, the specifications provided in Table 2 apply for FDP filled at 0.5, 1.0 or 2.0 g per vial. These specifications apply to FDP at release and over its shelf-life.

5. The BLA contains results of release analyses of (b)(4) FDP batches (representative of (b)(4) intermediate blends, (b)(4) fill (b)(4) , manufactured from (b)(4) batches of spray-dried fibrinogen and (b)(4) batches of spray-dried thrombin. The results for all batches are within FDP release specifications. In-support testing confirmed the suitability of the critical test methods for their intended use as release tests.

6. The stability program for Raplixa included studies at long-term storage (25 ºC / (b)(4) conditions. The stability program is extensive and includes studies on FDP, spray-dried fibrinogen and spray-dried thrombin, and intermediate blend. The available stability data revealed no negative

trends during the observed long-term storage period. The data support the proposed shelf-life of 24 months for Raplixa final container when stored at 25 ± 2 °C / (b)(4) The dating period for Raplixa should not exceed the dating periods for spray-dried thrombin and fibrinogen intermediates (whichever is the earliest) when stored at 25 °C. The dating periods for spray-dried thrombin and fibrinogen intermediates shall be 24 months from the date of (b)(4) when stored at 25 °C, and shall not exceed the manufacturer-specified expiration dates for these (b)(4) .

## INTRODUCTION

ProFibrix, BV (ProFibrix), a wholly owned subsidiary of The Medicines Company, Inc. submitted an original Biologics License Application (BLA) to seek U.S. licensure for Fibrin Sealant (Human). The active components in this product are fibrinogen and thrombin derived from human plasma collected in the U.S. from healthy donors. These biological components are (b)(4) using a manufacturing process that consists of validated virus inactivation and removal steps. The (b)(4) proteins are formulated, sterile-(b)(4), and spray-dried separately under aseptic conditions.

The sterile, spray-dried powders are then blended, and the mixture is filled in single-use glass vials and packed in a foil pouch. Each vial is filled with 0.5, 1 or 2 g of a mixture containing nominally 79 mg/g of fibrinogen and 699 IU/g of thrombin. The powder is applied directly, from the vial or using an optional spraying device, onto a bleeding site. The product dissolves in blood and starts the reaction between fibrinogen and thrombin, which results in the formation of blood clots and stops the bleeding. The proprietary name of the U.S. marketed product is Raplixa.

Raplixa is indicated as an adjunct to surgical hemostasis for mild to moderate bleeding from small vessels when control of bleeding by standard surgical techniques is ineffective or impractical. Raplixa may be used in conjunction with an absorbable gelatin sponge (USP).

## BACKGROUND

Fibrin sealants mimic the final stage of the blood coagulation cascade via the reaction of thrombin and fibrinogen at the site of bleeding to form a fibrin clot. The two-component fibrin sealants, in (b)(4) , have a long history of clinical use, including FDA-licensed products – TISSEEL and ARTISS (Baxter Healthcare Corp.), and EVICEL (Omrix Biopharmaceuticals, Ltd.). Additionally, two products representing fibrin sealant patch, for which thrombin and fibrinogen are embedded into an absorbable backing layer, are licensed in the U.S. - EVARREST by Omrix Biopharmaceuticals and TachoSil by Takeda Pharmaceuticals International.

The underlying concept for Raplixa is to blend fibrinogen and thrombin in a ready-to-use powder form, which can be stored at room temperature and applied directly onto a wound surface without the need for reconstitution or mixing. The manufacturing of a powder with the desired physical properties was achieved by proper formulation and utilization of a spray drying process. Fibrinogen and thrombin are (b)(4) a trehalose (b)(4) , sterile (b)(4) and spray-dried separately under aseptic conditions. The resultant (b)(4) are subsequently blended.

Upon application of the powder onto the bleeding site, the product dissolves in blood allowing for thrombin to react with fibrinogen resulting in the formation of fibrin clots that stop the bleeding. Raplixa is the first biological product manufactured by spray drying.

Both biological components of Raplixa, human fibrinogen and human thrombin, are manufactured by (b)(4) and licensed by the FDA. Fibrinogen is licensed for the treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency (b)(4) and Thrombin is licensed (b)(4) of Raplixa.

Raplixa is manufactured at (b)(4) The FDP manufacturing process is comprised of spray drying of fibrinogen and thrombin, followed by blending, vialing and packaging.

Raplixa was developed under Investigational New Drug (IND) application, IND 14385, originally submitted by ProFibrix in September 2010. ProFibrix was acquired by The Medicines Company in August 2013 and continues to operate as a wholly owned subsidiary, with the Medicines Company being the U.S. agent.

Raplixa is not currently approved or marketed in any other countries. On 22 January 2015, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending the granting of a marketing authorization for Raplixa in the European Union.

## REVIEW SUMMARY

### Modules reviewed (including relevant documents supplied in appendices and amendments):

Module 3 except section 3.2.P.5.2 Analytical Procedures and section 3.2.P.5.3 Validation of Analytical Procedures (The review of these sections was performed by Dr. Natalya Ananyeva and documented in her memo.)

### Review History

The BLA was submitted electronically on 31 January 2014, and reviewed under the standard 12-month review schedule of the PDUFA V program.

During the review, FDA requested ProFibrix to make substantial revisions to the Final Drug Product Specifications and provide justifications for the specifications based on the company's manufacturing experience. In response, ProFibrix submitted Amendment 16 on 17 October 2014, which contained a large amount of new information. This submission was classified as a Major Amendment, and the action due date was extended to 2 May 2015.

Information Requests (IR) from this reviewer were sent on 10 September 2014, 23December 2014 and 19 March 2015.

**Table 1: Review Milestones**

| Milestone | Date |
|---|---|
| Received | 31 January 2014 |
| Filed | 1 April 2014 |
| Mid-Cycle Communication | 30 July 2014 |
| Major Amendment | 17 October 2014 |
| Late-Cycle Meeting | Cancelled by the company |
| Action Due Date | 2 May 2015 |

This reviewer also participated in the pre-license inspection of (b)(4) conducted on (b)(4) .

**Narrative:**

**MANUFACTURING PROCESS**

The manufacturing process for FDP is described in section 3.2.P.3.3 in the BLA. The process flow was demonstrated during the Pre-License Inspection (PLI) of (b)(4) conducted on 22-29 September 2014. The process diagram is presented in **Figure 1.**

The Raplixa FDP is manufactured at (b)(4) . The FDP manufacturing process is comprised of spray drying separately of the formulated and sterile-(b)(4) fibrinogen and thrombin solutions to form (b)(4) of a desired size; followed by blending of the two protein powders; and filling of the mixture in single-use vials. These operations are performed under aseptic conditions.

Raplixa is manufactured from (b)(4) ) - Thrombin ((b)(4) and Fibrinogen (b)(4) (Human) - supplied by (b)(4). Other components in the FDP are trehalose and calcium chloride.

Thrombin is (b)(4) with a trehalose/ (b)(4) and fibrinogen is (b)(4) with a trehalose (b)(4) . (b)(4)

(b)(4)

.

(b)(4)

1 page determined to be not releasable: (b)(4)

(b)(4)

Sterile-(b)(4) thrombin and fibrinogen (b)(4) are spray-dried separately into a powder using (b)(4) .

The spray-dried thrombin and fibrinogen powders are (b)(4) and sealed in aluminum pouches.

The spray-dried thrombin and fibrinogen powders are blended using an (b)(4) The target fill weight is 0.5, 1.0 or 2.0 g/vial. The vials are (b)(4) stoppered, (b)(4) over-sealed, visually inspected, labeled, and sealed in a foil pouch. All steps from blending to pouching occur aseptically in a Class (b)(4) .

***Reviewer's Comments (all italicized text in the rest of the memorandum represents this reviewer's comments):***
*The unit operations and process controls are designed to allow for adjustment of process parameters during manufacture to minimize wastage of raw materials and the potential of failure of the FDP. The use of (b)(4) for all critical steps of the manufacturing process significantly reduces the risk of product contamination and allows for a well-controlled environment and improved process consistency.*

**SOURCE MATERIAL/(b)(4) QUALITY AND CONTROL**

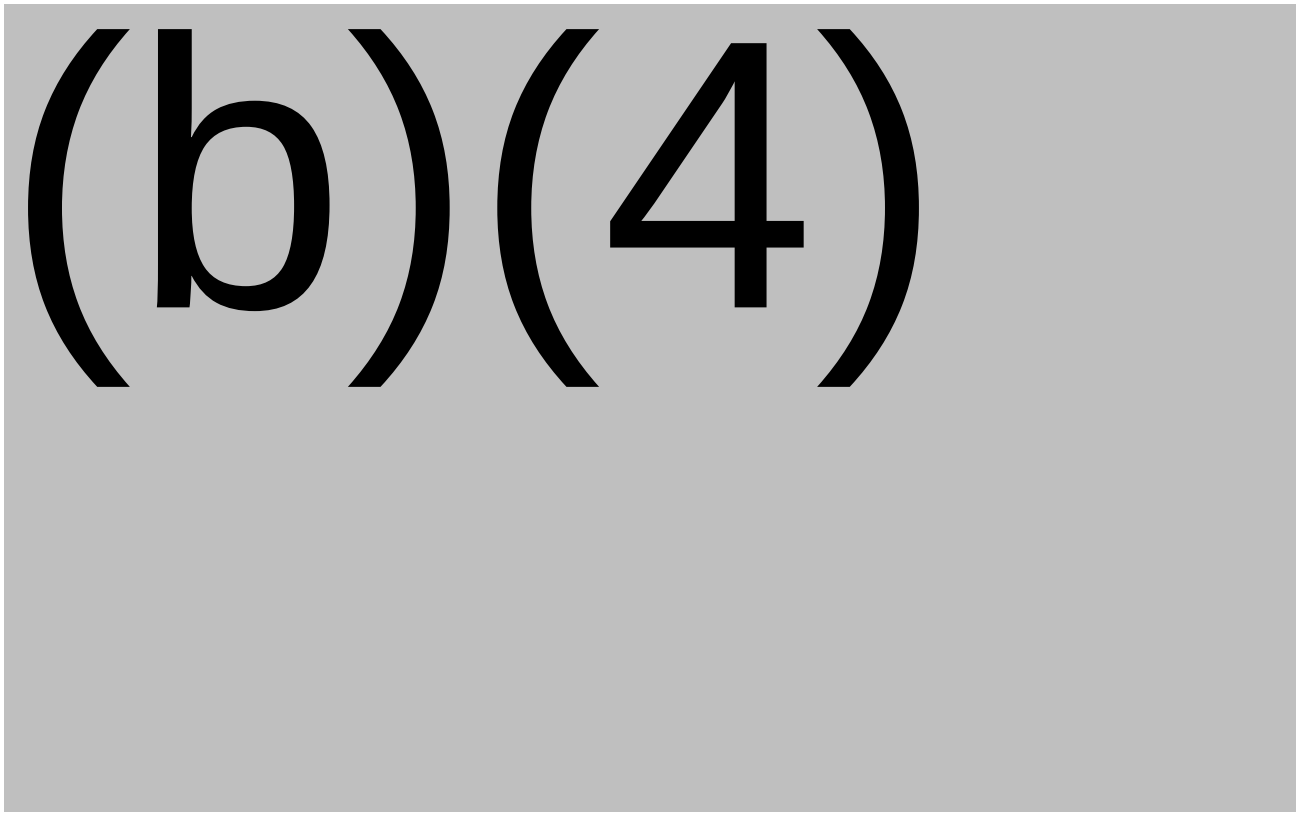
Both (b)(4) used in Raplixa, human fibrinogen and human thrombin, are manufactured by (b)(4) and licensed by the FDA.

(b)(4) thrombin is supplied by (b)(4) in vials with a (b)(4) . Upon receipt, the *Certificate of Analysis* (CoA) is checked for compliance with raw material specification, and thrombin (b)(4) are tested at (b)(4) by (b)(4) by (b)(4) (**Table 2**).

(b)(4) fibrinogen is supplied by (b)(4) in vials with a (b)(4) . Upon receipt, the CoA is checked for compliance with raw material specification, and fibrinogen (b)(4) are also tested at (b)(4) (**Table 3**).

The shipping of fibrinogen and thrombin (b)(4) was validated, monitored, and controlled by (b)(4).

(b)(4)




*Per FDA's request, the acceptance criteria for fibrinogen content and thrombin potency were revised based on previous experience to allow for better control over potential degradation of these proteins during shipping and storage. The initial specifications included wide fixed ranges of values for thrombin potency and fibrinogen content. Changes of the acceptance criteria for* (b)(4) *difference of* (b)(4) *result from* (b)(4) *CoA value"*

Trehalose and calcium chloride are supplied as (b)(4) from qualified vendors (b)(4) , respectively). Upon receipt, the CoAs are checked for compliance with raw material specifications, and the materials are tested for (b)(4) . Trehalose is tested using (b)(4) .

*The quality control procedures and specification for raw materials and* (b)(4) *are adequate.*

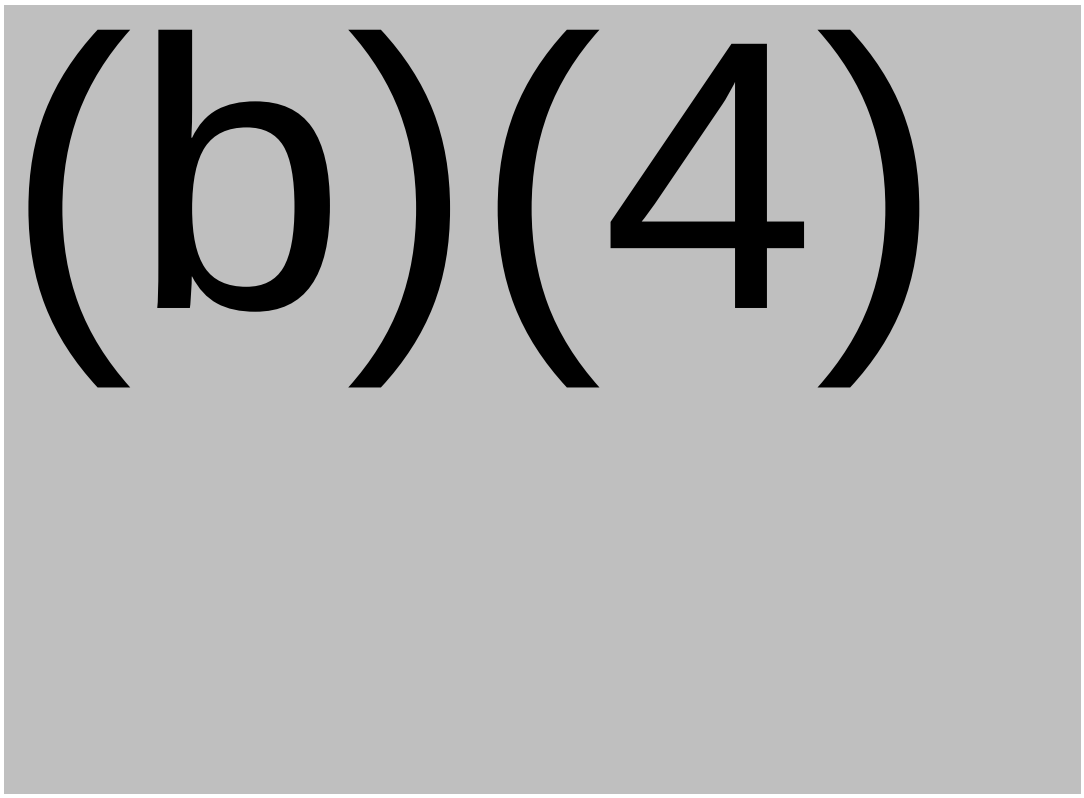
**CHARACTERIZATION**

The mechanisms of action of fibrin sealants are well studied and the (b)(4) fibrinogen and thrombin (b)(4) have been reviewed in previous applications, therefore, the active components do not require additional characterization. However, in other fibrin sealant products, the thrombin and fibrinogen components are filled and stored separately to avoid premature reaction before their application to a bleeding site. In Raplixa, the fibrinogen and thrombin powders are

blended, vialed, stored at room temperature, and can be applied onto a bleeding or oozing wound without the need of reconstitution or mixing. This is achieved by proper formulation and spray drying. Since this is the first application of spray drying to manufacture a biological product, characterization studies were undertaken to evaluate the effects of spray drying on the structural and functional properties of fibrinogen and thrombin, the stability of the blend, and the physical properties of the powder.

Structural (b)(4) of fibrinogen and thrombin and absence of premature conversion of fibrinogen to fibrin were confirmed by (b)(4) (for fibrinogen) and (b)(4) (for thrombin) (b)(4)

(b)(4)

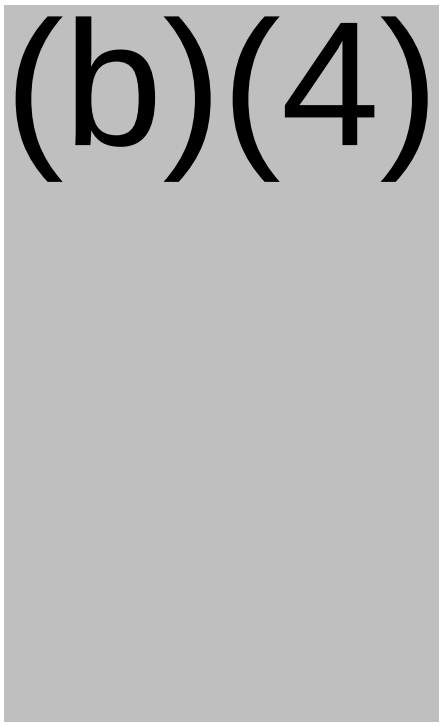



(b)(4)

1 page determined to be not releasable: (b)(4)

(b)(4)

(b)(4)




(b)(4)

To determine the particle size distribution of the spray-dried particles, a (b)(4)

Additionally, although thrombin is supplied by (b)(4) and is a licensed product, ProFibrix performed characterization on this material, including analysis of (b)(4) ratio by (b)(4), characterization of protein (b)(4), and characterization of (b)(4).

An in-depth characterization of the (b)(4) thrombin was triggered by discrepancy in thrombin (b)(4) calculated from the CoA parameters from (b)(4) of other thrombin standards. (b)(4) was determined by the (b)(4);

and thrombin activity by a (b)(4) as specified by (b)(4). Calculating the (b)(4) of the (b)(4) based on the CoA data, resulted in a (b)(4) of about (b)(4) total protein for any given lot, which was significantly lower than the reported (b)(4) for the thrombin standards, e.g., (b)(4)

One possible explanation for this discrepancy was that only the (b)(4) component is active in the clotting assay while other thrombin (b)(4), such as (b)(4), contribute to the total protein concentration. So, the amount of (b)(4) present in the (b)(4) active substance was determined using an (b)(4). The clotting activity of the (b)(4) component was also assessed using a (b)(4)) assay. Using both the (b)(4) values, (b)(4) were calculated for several (b)(4) thrombin lots. The results demonstrated that the average (b)(4) for (b)(4) was about (b)(4), which is in line with the expected thrombin (b)(4).

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

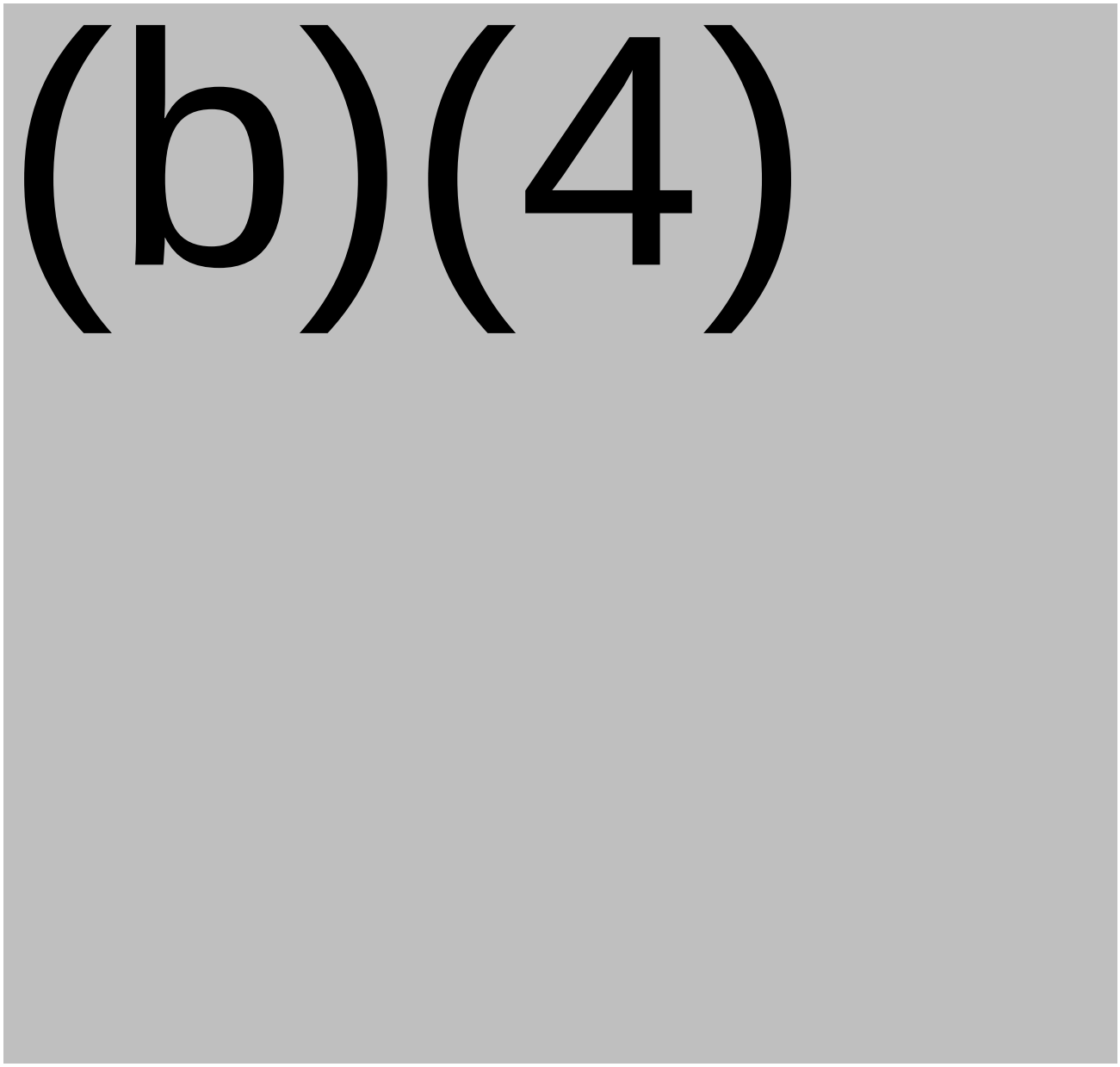
(b)(4)

*The company performed a thorough characterization of the product to confirm that the spray-drying process does not significantly affect the structure and function of the protein components. The critical concern – pre-mature activation of fibrinogen - was satisfactorily addressed by the characterization study results.*

(b)(4)

(b)(4)

(b)(4)




The timeline of manufacturing process development is presented in **Table 4** above. The Raplixa drug product concept was based on the use of spray-drying and the advantages allowed by this process. As a result, the initial manufacturing development was mostly centered on the technical details of the process, namely, evaluating the various spray-drying operation parameters and formulation in order to achieve the target product quality attributes.

(b)(4) major manufacturing changes during the development included the change in the supplier of the fibrinogen and (b)(4) .

The (b)(4) supplier was change after (b)(4) batches were manufactured with (b)(4) The manufacturing process remained essentially the same. No change in the

(b)(4) concentration of fibrinogen and thrombin was implemented. Pharmacology and toxicology studies demonstrated that the product manufactured using the (b)(4) had the expected pharmacology in several animal models for bleeding, and was found to be non-toxic. The effect of this change on product quality, safety and effectiveness was minor.

The change of the FDP manufacturer from (b)(4) was associated with process (b)(4) spray-dried batch. In addition, several major changes were introduced to the process, which were associated with changes in product potency, without changes in the amounts of (b)(4) used. The changes are as follows:

1. (b)(4)
2. (b)(4)
3. (b)(4)
4. (b)(4)

ProFibrix compared the (b)(4) product and the (b)(4) aseptically manufactured product. In addition to the characterization methods described under **CHARACTERIZATION**, the studies included a (b)(4) of particles, and (b)(4) test and (b)(4) of fibrin clot. All test results demonstrated comparability between Raplixa batches used in the nonclinical and clinical studies and the commercial product. The material used in Phase 3 clinical trials is representative of that manufactured by the commercial manufacturing process.

A review of the proposed commercial manufacturing process was conducted which included a (b)(4) risk assessment of all manufacturing operations and process steps. A risk scoring system was used to determine the areas which posed a high risk to the identified CQAs, safety (cross contamination) or sterility of the intermediates or FDP.

Critical process parameters having direct impact on product quality attributes have been identified, and operating parameter ranges established to ensure an appropriate level of control is applied. Based on a risk assessment of the complete manufacturing process, additional manufacturing controls were integrated into manufacturing operations that were identified to present a high level of risk to the potency, efficacy, sterility or safety of the FDP. As a result of these improvements, the process is adequately controlled.

**IN-PROCESS CONTROLS**

Early development studies and risk management tools were used to identify critical process parameters (CPPs) and manufacturing unit operations that can impact the critical quality attributes (CQAs) of the intermediates and FDP. The obtained information was used to develop in-process controls for the manufacturing process and FDP specifications. Each process parameter was evaluated to assess its impact on the identified CQAs. All CPPs were defined in this way, and control strategies were then developed and implemented.

Since the quality of the Raplixa FDP is highly dependent on the efficiency of the spray drying process and blending of the thrombin and fibrinogen powders, the controls for these intermediates are critically important. The extensive specification for spray-dried fibrinogen and thrombin were established (see **Tables 5 and 6**).

(b)(4)

(b)(4)

1 page determined to be not releasable: (b)(4)

(b)(4)

Since the intermediate blend is produced by simply blending (b)(4) parts of spray-dried powders of fibrinogen and thrombin, the specification for the intermediate blend is limited to (b)(4) controls (**Table 7**).

(b)(4)

(b)(4)

*As requested by the FDA, the justifications for the specifications of in-process controls were re-evaluated and the acceptance criteria were revised based on manufacturing experience for the following parameters:* (b)(4) *The initial specifications for these parameters were set up arbitrarily and were not justified by the actual test results.*

*Subsequently, the following values were suggested by the FDA and accepted by the company, based on the analysis of the data provided by ProFibrix:*

(b)(4) *)*

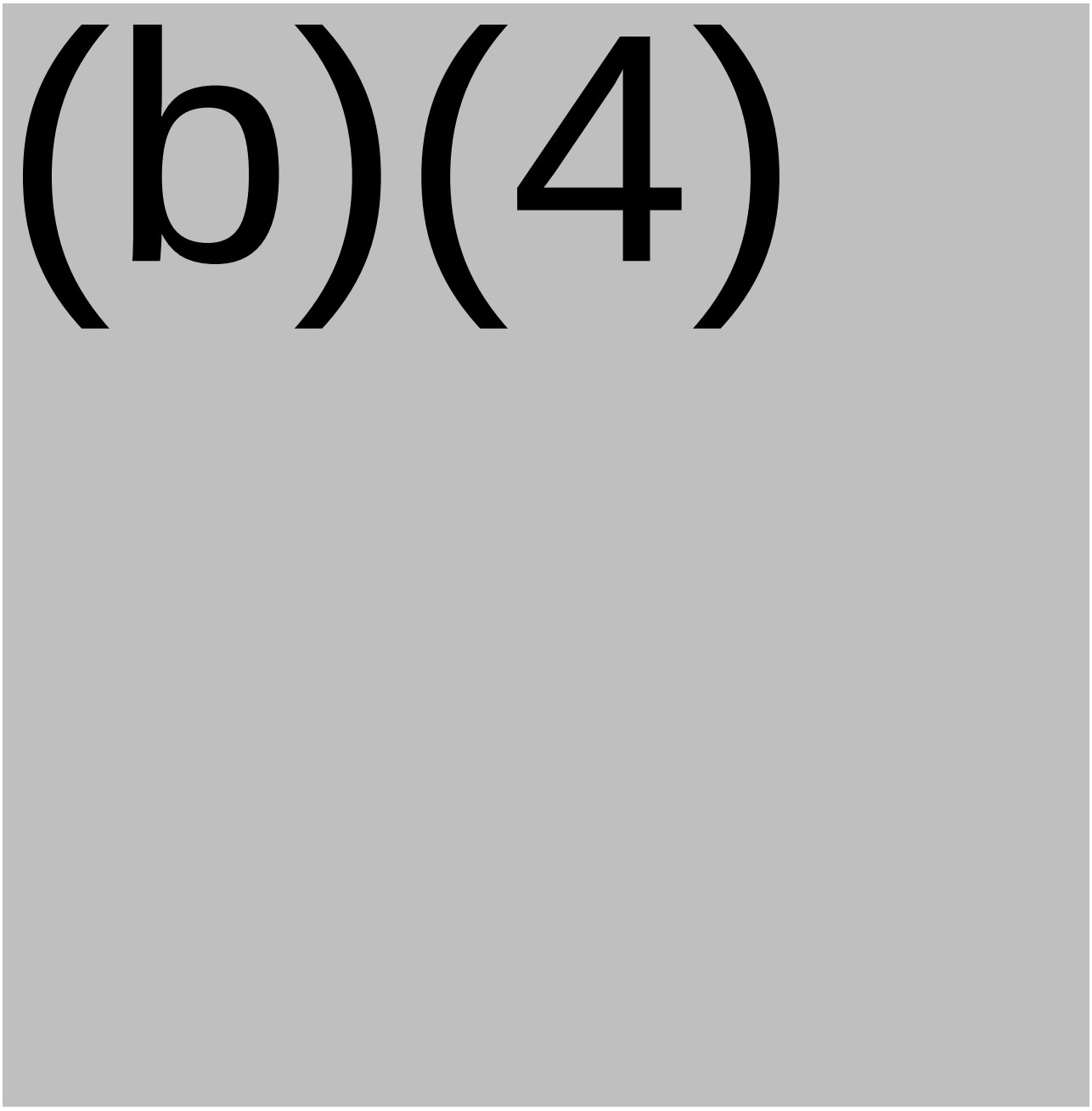
(b)(4)

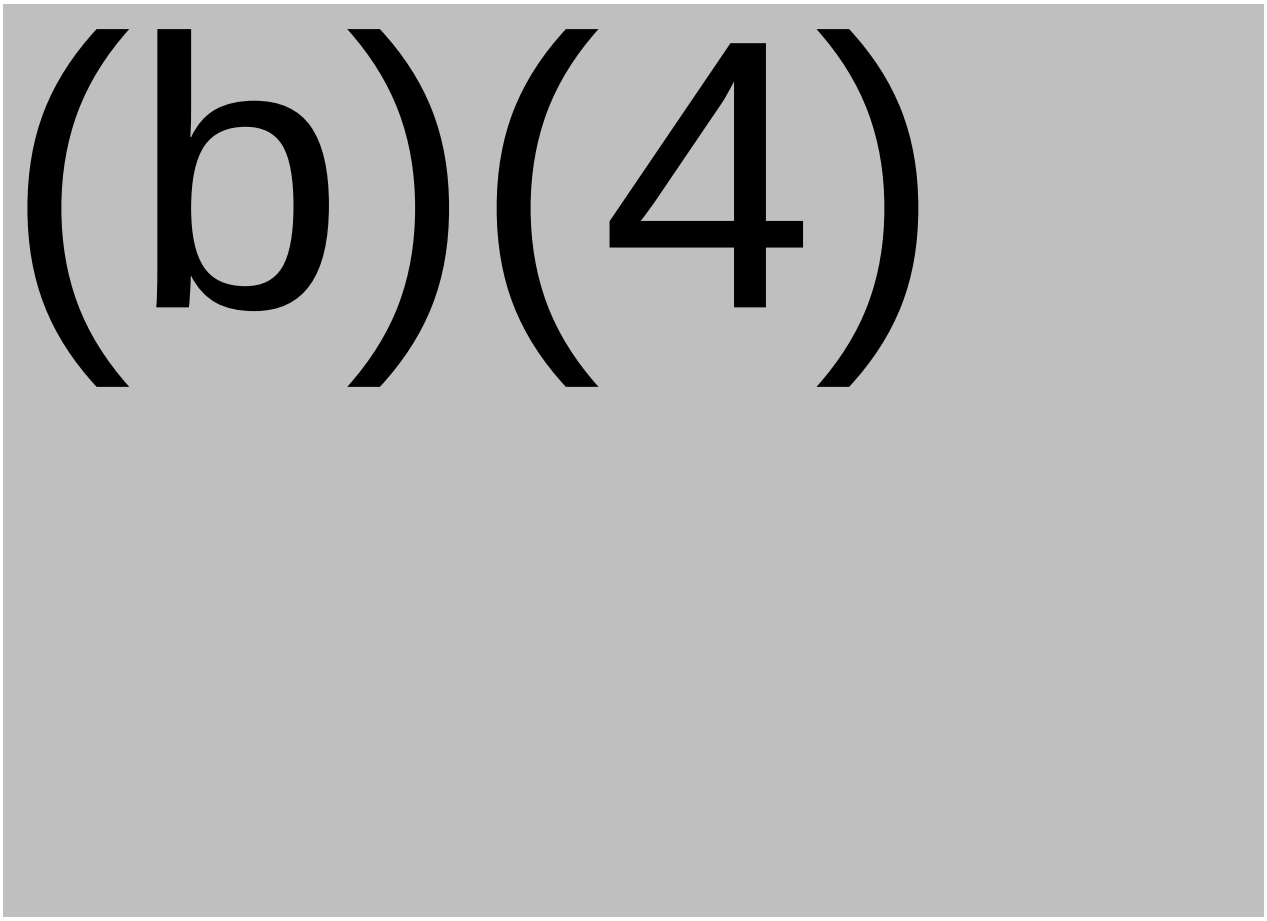
(b)(4)

*Additionally, the possibility to add the in-process control specifications for* (b)(4) *and* (b)(4) *was considered and discussed with the company. As requested by FDA, tests for* (b)(4) *were validated and performed on PPQ batches to confirm that these parameters are consistent with the theoretical content, and between batches. The nature of the manufacturing process, provided data and the fact that other in-process control parameters act as surrogate controls for* (b)(4) *deemed these in-process control specifications redundant.*

The full list of in-process controls in Raplixa manufacture is presented in **Table 8**.

(b)(4)






All in-process hold times were validated in prospective stability studies (see **VALIDATION OF MANUFACTURING PROCESS** section) that demonstrated that the CQAs of the intermediates were not negatively affected during the established time periods.

*The in-process controls are extensive and tied to the CQAs. We found the CPPs and in-process control specifications to be adequate to provide control over the process to manufacture product lots of consistent yield, purity and potency.*

**VALIDATION OF MANUFACTURING PROCESS**

ProFibrix has adopted a (b)(4) process validation approach which is based on their understanding of the process and experience accumulated during product development performed at both (b)(4) (Phase 3 and commercial manufacture).

- (b)(4)

- (b)(4) .

- (b)(4)

The commercial manufacturing process has been defined using a development strategy based on the principles of (b)(4) Emphasis was put on using information gained from process development studies to identify potential CQAs of spray-dried fibrinogen and thrombin and intermediate blends that were linked to the CQAs of Raplixa FDP.

Risk management and data evaluation were subsequently used to identify the CPPs and the unit operations that could impact the CQAs of Raplixa FDP and its intermediates. Following its design, review of the manufacturing process and risk assessment of all steps were performed to identify control strategies to ensure consistent, reproducible process performance and FDP quality.

To demonstrate the capability of the aseptic process to consistently manufacture sterile FDP, an aseptic process simulation (APS; also referred to as media fills) program was carried out.

The program consisted of (b)(4) initial consecutive successful media fills, simulating the manufacturing operations. These initial media fills were executed successfully prior to the PPQ batches. Revalidation of the aseptic processes is performed (b)(4) (defined as (b)(4) media fills performed in the previous (b)(4) prior to batch manufacture).

The APS program was designed to simulate all aseptic manufacturing operations and to identify key contamination risk factors that could occur during the manufacturing operations and thereby accurately assess the state of control throughout the process.

Worst-case factors (e.g., interventions, duration, shifts) were used to design the media fill to ensure the simulation presents a reasonable challenge to the system without forcing unintentional failure as stipulated in the guidelines.

Media fills were used to establish validated ranges, shown in **Table 9**. The minimum aseptic processing times and number of filled vials are taken from the (b)(4) media fills. These parameters were used in the manufacture of PPQ batches as shown in **Table 10.**

(b)(4)

(b)(4)

2 pages determined to be not releasable: (b)(4)

(b)(4)
.

**SPECIFICATION FOR FINAL DRUG PODUCT**

The specification for Raplixa FDP is established in accordance with ICH Guidelines Q6A and Q6B. The parameters are selected from CQAs determined in the process development studies and risk assessments. Acceptance ranges/limits are established based on manufacturing capability, clinical outcome, analytical variability, and stability data. Manufacturing capability was assessed through analysis of release data for the Phase 3 clinical and process validation batches. The following substantive issues were resolved in the course of the review:

*Justification of Specification*
*Justification of Specification for Raplixa FDP submitted in the original BLA was deemed insufficient. Initially, the key parameters of specification were established arbitrarily and were not based on manufacturing capability.*

*As requested by FDA, ProFibrix re-evaluated the ranges and limits for all quantitative parameters in the specification based on statistical analysis of data acquired from testing all FDP lots. As a result of the change in the thrombin potency specification from* (b)(4) *, the nominal thrombin potency of the FDP was changed from* (b)(4) *The change was made to preserve the compliance of the product with* (b)(4) *for fibrin sealants, which specifies that the specification for thrombin potency should be* (b)(4) *from nominal potency. Since the current specification limits were established based on the manufacturing experience of clinical and PPQ lots and are acceptable to FDA, and the change in the nominal potency is not associated with changes in the manufacturing process, this reviewer has no objections to the change.*

*In the revised specification, some acceptance criteria were still not consistent with the manufacturing experience. The following values were suggested by the FDA and accepted by the company, based on the analysis of the data provided by ProFibrix:*

*Fibrinogen potency:* (b)(4) *based on the provided data)*
*Fibrinogen content:* (b)(4) *based on the provided data)*
*Moisture content:* (b)(4)
*Endotoxin:* (b)(4) *(considering that all data were below the method LOQ of* (b)(4)

(b)(4)

(b)(4)

**Table 12. Specification For Final Drug Product**

| Test | Method | Specification for Release and Stability |
|---|---|---|
| Appearance | Visual Determination of Appearance | White to off-white powder, no visible agglomerates |
| Identity Fibrinogen | (b)(4) | (b)(4) |
| Identity Thrombin | (b)(4) | (b)(4) |
| Fibrinogen potency | (b)(4) | (b)(4) |
| Thrombin potency | (b)(4) | (b)(4) |
| Fibrinogen content (b)(4) | (b)(4) | (b)(4) |
| Thrombin content (b)(4) | (b)(4) | (b)(4) |
| Fibrinogen content | (b)(4) | (b)(4) |
| Thrombin content | (b)(4) | (b)(4) |
| Moisture content | (b)(4) | (b)(4) |
| Total protein content | (b)(4) | (b)(4) |
| (b)(4) | (b)(4) | (b)(4) |
| Fibrinogen integrity | (b)(4) | (b)(4) |
| Fibrinogen integrity | (b)(4) | (b)(4) |
| Premature fibrinogen (b)(4) | (b)(4) | (b)(4) |
| Thrombin integrity | (b)(4) | (b)(4) |
| Sterility | (b)(4) | (b)(4) |
| Pyrogenicity | (b)(4) | (b)(4) |
| Endotoxin | (b)(4) | (b)(4) |

*The final FDP Release Specification, as summarized in **Table 12**, is considered adequate to control the identity, purity, activity, and safety of Raplixa. As the specification is* (b)(4) *based, the specifications provided in **Table 12** apply to FDP filled at 0.5, 1.0 or 2.0 g per vial. These specifications are used both for FDP release and monitoring of product stability throughout its shelf-life.*

## DESCRIPTION AND COMPOSITION OF DRUG PRODUCT

Raplixa is supplied as a sterile, spray-dried, ready-to-use powder in single-use glass vials packed in a foil pouch. Each vial is filled with 0.5, 1 or 2 g of the product containing nominally 79 mg/g of human fibrinogen and 699 IU/g of human thrombin.

In addition to fibrinogen and thrombin, 824 mg/g trehalose and 11 mg/g calcium chloride were added to manufacture the FDP. The following components are carried over to Raplixa FDP as part of the formulations in the fibrinogen and thrombin (b)(4) human albumin, (b)(4) sodium chloride, (b)(4) sodium citrate, and (b)(4) L-arginine hydrochloride.

The product may be delivered using an optional gas operated RaplixaSpray device. The device comes in a kit, containing separately a sterile-packed sprayer with attached rigid nozzle, flexible nozzle, and air filter. The 510(k) application BK # 140119/0 was submitted for the device and it is going to be cleared concurrently with the approval of Raplixa BLA.

### Container Closure System

The container closure system for Raplixa consists of the following components:

- 6-mL clear (b)(4) glass vial (b)(4) Type (b)(4) glass specification
- (b)(4) rubber stoppe (b)(4)
- (b)(4) white crimp seal ('Flip Tear Up') consisting of an aluminum shell (b)(4)
- (b)(4) / Aluminum/ (b)(4) ) peel-able foil pouch (b)(4) . This material meets the requirements of ISO 11607-1.

## CBER LOT RELEASE

Raplixa is manufactured from human plasma-derived proteins and is subject to routine lot-by-lot release by CBER. The *Lot Release Protocol* for the FDP is submitted as part of the BLA and is found to be adequate.

The following tests will be performed by DBSQC as part of the lot release:

Fibrinogen potency –(b)(4) protein (manufacturer's method)
Thrombin potency –(b)(4) assay (manufacturer's method however using the(b)(4) as reference)
Thrombin content –(b)(4) (manufacturer's method however using the (b)(4) as reference)
Moisture content – (b)(4)
Endotoxin

**STABILITY**

The batch release assays that are used as stability indicating assays are outlined in **Table 13** for spray-dried fibrinogen and thrombin, intermediate blend, and FDP. Stability indicating parameters are based on the CQAs.

In general, the stability indicating assays for spray-dried fibrinogen, spray-dried thrombin, and intermediate blend are a subset of assays used for FDP release. The assays were selected on the CQAs that are most meaningful to track the stability and integrity of the spray-dried fibrinogen and thrombin and intermediate blend.

The stability program for Raplixa included studies under long-term storage (25 ºC / (b)(4) conditions. The stability program is extensive and included studies on the FDP, spray-dried fibrinogen, spray-dried thrombin, and the intermediate blend.

Stability studies (as of January 20, 2015- the date of submission of Amendment 24 to the BLA) include:

1. (b)(4) batches of spray-dried intermediates(b)(4) for each spray-dried(b)(4) For each intermediate (thrombin and fibrinogen), (b)(4 different (b)(4) lots were used. All batches were placed at 25 ± 2°C /(b)(4) in sealed glass vials and pouched.

2. (b)(4 development batches of intermediate blend were placed on storage at 25 ± 2 °C / (b)(4) product packaged in glass collection bottles and pouched.

3. (b)(4 PPQ intermediate blends (b)(4) stored at full scale a (b)(4) within the (b)(4) prior to commencement of filling within the (b)(4) .

4. (b)(4 development drug product batches, manufactured at blend (b)(4) at 1.0 g per vial. These development batches were manufactured as part of (b)(4)

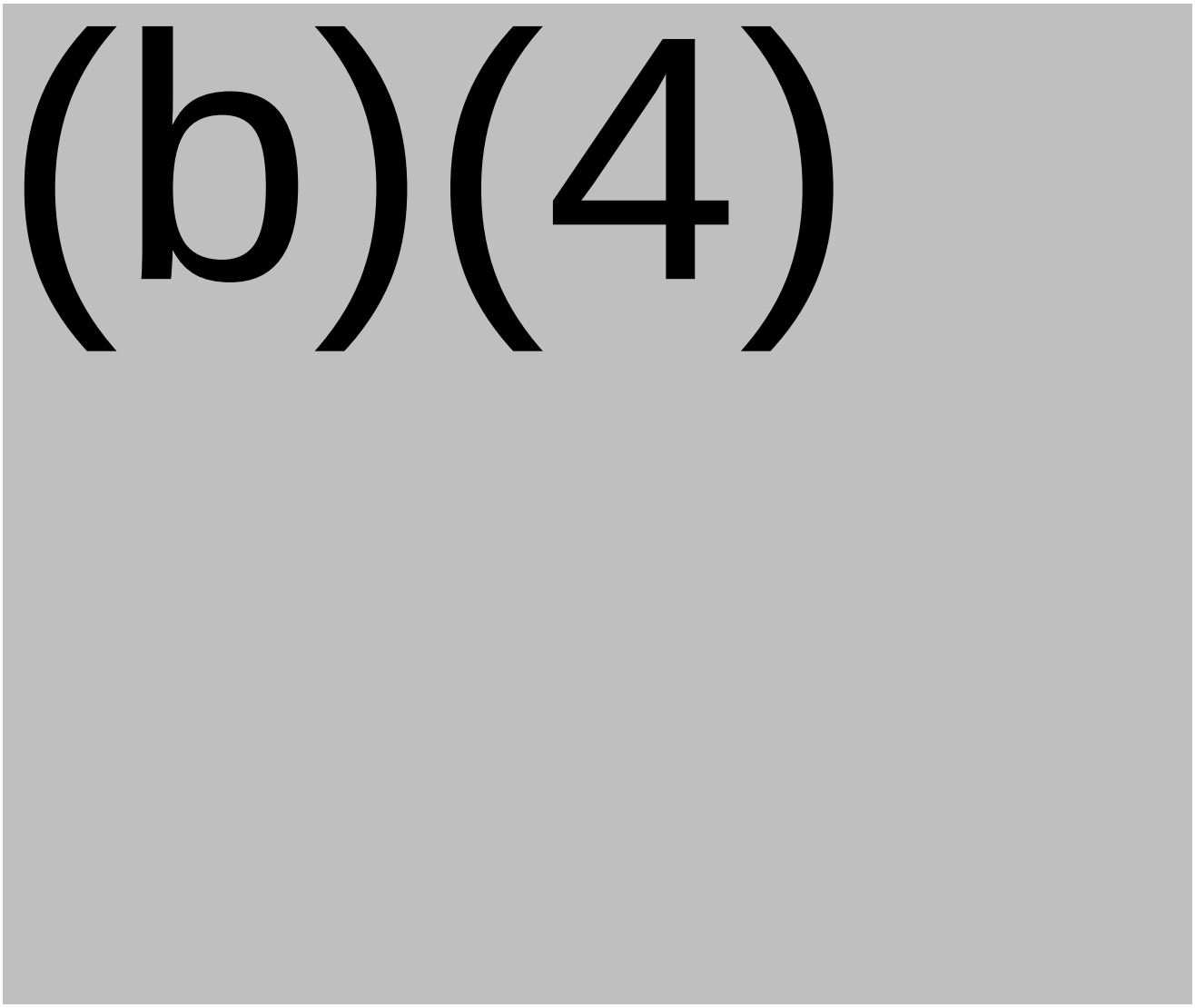
5. (b)(4 development batch, filled at 1.0 g per vial, manufactured at a (b)(4) under GMP.

6. (b)(4) PPQ drug product batches, filled at 1.0 g per vial, manufactured at the (b)(4)

7. (b)(4) development drug product batches (one filled at 0.5 g per vial and one filled at 2.0 g per vial ), manufactured from PPQ (b)(4) spray dried thrombin and fibrinogen and at a (b)(4) of (b)(4)

8. (b)(4) drug product batches filled at 0.5 g and 2.0 g per vial (two for each configuration) manufactured as part of the (b)(4) blends of (b)(4)

(b)(4)




All drug product batches were placed on storage at (b)(4) 25 ± 2°C / (b)(4)

No photo-stability studies were performed, as the product vials are packed in foil pouches and the FDP is not exposed to light until the vial is removed from the carton and pouch.

The available stability data revealed no negative trends during the observed long-term storage period. The data support the proposed shelf-life of 24 months for the Raplixa final container when stored at 25 ± 2 °C / (b)(4)

The intermediate blends of the PPQ batches (b)(4) stored at full (b)(4) also consistently show results that meet the pre-determined specifications over a (b)(4) storage period.

*Several OOS results were observed in the stability studies for FDP and intermediates. The cause of OOS was not associated with product failure as no negative trends were observed. The two major reasons for OOS were identified:*

1. *Failure of the analytical procedures.*
   *The repeated OOS were observed during the pre-license inspection of* (b)(4) *and observation was included in Form FDA 483. In response to the observation, the company was able to significantly improve method performance (the details are in a separate memorandum).*

2. *The poor choice of acceptance criteria. As described under DRUG PRODUCT SPECIFICATION and IN-PROCESS CONTROLS sections of this memo, the initial acceptance criteria for some parameters were established arbitrarily and did not reflect manufacturing experience. When the acceptance criteria were re-established in response to FDA comments, these OOS values were actually within the specification limit.*

As supported by the studies, the dating period for Raplixa should not exceed the dating periods for spray-dried thrombin and fibrinogen intermediates (whichever is the earliest) when stored at 25 °C. The dating periods for spray-dried thrombin and fibrinogen intermediates shall be 24 months from the date of (b)(4) when stored at 25 °C, and shall not exceed the manufacturer-specified expiration dates for these (b)(4) .

In-use stability studies were performed a (b)(4) to simulate the worst-case scenario. Three lots of FDP were used for in-use stability studies. The tests performed and the results are summarized in **Table 14**.

The main factor affecting in-use stability is absorption of moisture by the FDP which results in the caking of the powder, and makes it difficult to apply the product to the wound (failure of appearance and powder delivery tests).

*The data support FDP in-use stability of 1 h after the vial is opened. ProFibrix claimed that the data support the use of FDP within* (b)(4) *after the vial is opened. However, the moisture content in the FDP lots used in these studies is only* (b)(4)*, which is significantly lower than the* (b)(4) *of the FDP specification. Thus, the label will state that the product should be used within 1 h after opening.*

**Table 14. The results of in-use stability study of Raplixa FDP.**

| Test | Meets acceptance criteria | |
|---|---|---|
| | 1 hr | (b)(4) |
| Moisture content | Y | |
| Appearance | Y | |
| Thrombin potency | Y | |
| Fibrinogen potency | Y | |
| Total protein | Y | |
| Fibrinogen integrity | Y | |
| Thrombin integrity | Y | |
| Powder delivery | Y | |

ProFibrix provided *Post-approval Stability Protocols* for spray-dried fibrinogen and thrombin and for FDP.

(b)(4)

.

(b)(4)

(b)(4)

*Post-approval Stability Protocols stability commitment are reviewed and found to be adequate to monitor FDP stability post approval.*